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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
MOORE, WILLIAM W	

ART UNIT	PAPER NUMBER
1656	

DATE MAILED: 10/11/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/763,619	RUMENAPF ET AL.	
	Examiner	Art Unit	
	William W. Moore	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 July 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *20040628 &20040723*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Priority

Applicant's claim in the Declaration of Inventorship and in the Amendment to the first page of the specification filed 23 January 2004 to priority under 35 U.S.C. § 119 of the 9 August 1999 filing date of the Austrian patent application No. 1368/99 and the 7 August 2000 filing date of PCT/EP00/07642, its successor International application, preserved by the filing of the intervening US patent application serial No. 10/048,872, is hereby acknowledged. In responding to this communication, Applicant is invited to amend lines 1 and 2 of page 1 of the specification to indicate the current status of the US patent application serial No. 10/048,872.

Information Disclosure Statement

Applicant's Information Disclosure Statements [IDS] filed on 28 June 2004 and 23 July 2004 are hereby acknowledged.

Preliminary Amendment

Applicant's several Preliminary Amendments to the specification and claims filed on 23 January 2004, 28 June 2004, and, most recently, 17 July 2006, have been entered. Claims 1-13 are examined herein.

Claim Objections

Claims 8-13 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim cannot depend from any other multiple dependent claim. See MPEP § 608.01(n). While an early preliminary amendment removed the impermissible multiple dependencies of claims 8-13, clarifying their intended subject matter, the most recent claim amendment of 17 July 2006 inadvertently re-introduced the multiple dependencies of claims 8-13. Nevertheless, claims 8-13 are further treated on the merits herein but must be amended to remove the impermissible dependencies.

Claims 4-6 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim, claim 3. Applicant is required to cancel the claims, or amend the claims to place the claims in proper dependent form, or rewrite the claims in independent form. Because each of claims 4-6 recite, "or a derivative thereof with autoproteolytic activity", but provide no indication of any derivative structure that is distinguishable from the amino acid sequence of a bovine viral diarrhea virus N^{PRO} autoprotease, or from the amino acid sequence of a border disease virus N^{PRO} autoprotease, claims 4-6 describe subject matter exceeding the scope of the classical swine fever virus N^{PRO} autoprotease of claim 3. Amending claims 4-6 to delete the phrase, "or a derivative thereof with autoproteolytic activity", would place them in proper dependent form.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claim 13 is rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-9 of the commonly assigned U.S. Patent No. 6,936,455. Although the conflicting claims are not identical, they are not patentably

distinct from each other because the pending claim 13 is drawn to a process, or method, described more particularly by the patented claims 1-9.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-13 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

While the specification discloses a set of proteolytically active fragments of the classic swine fever virus N^{PRO} autoprotease of SEQ ID NO:1, and Wiskerchen et al., made of record with Applicant's Information Disclosure Statement, teach several amino acid sequence modifications of a pestivirus N^{PRO} autoprotease that either abolish or retain its autoproteolytic activity, the specification fails to exemplify or describe the preparation of the divergent pestivirus N^{PRO} proteases commensurate in scope with the terms "has the autoproteolytic function of" and "derivative thereof with autoproteolytic activity". These terms recited in, e.g., claims 1 and 4-6, exceed deletions of the amino-proximal regions recited in claims 5 and 5 and exceed the introduction of one or few amino acid substitutions because they reach derivatives that need have no particular, or limited, structural relationship to, e.g., the amino acid sequence set forth in SEQ ID NO:1. Where Wiskerchen et al. were able to identify an amino acid essential to the autoproteolytic activity of a pestivirus N^{PRO} autoprotease, they were unable to identify the set of amino acids, and their relationship in the primary structure of a pestivirus N^{PRO} autoprotease, that are sufficient to maintain autoproteolytic activity and the specification provides no disclosure that supports the non-specific derivatization of pestivirus N^{PRO}

autoprotease amino acid sequences. "While one does not need to have carried out one's invention before filing a patent application, one does need to be able to describe that invention with particularity" to satisfy the description requirement of the first paragraph of 35 U.S.C. § 112. *Fiers v. Revel v. Sugano*, 25 USPQ2d 1601, 1605 (Fed. Cir. 1993). The specification's treatment of the subject matter of the clauses in claims that are the subject of this rejection, and claims 2, 3, and 7-13 that depend thereon, is considered to be entirely prospective where skilled artisans in the relevant field of molecular biology could not predict the structure, or other properties, of the derivative pestivirus N^{PRO} autoproteases of claims 1 and 4-6.

Claims 1-13 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for the preparation of a fusion polypeptide comprising an amino-proximal pestivirus N^{PRO} autoprotease having an amino acid sequence that corresponds to the amino acid sequence from position 22 through position 168 of SEQ ID NO:1, whereby a fusion partner carboxyl-proximal to the pestivirus N^{PRO} autoprotease region may be autoproteolytically processed to produce a free protein that is not a pestivirus protein, i.e., a free heterologous protein,

does not reasonably provide enablement for the preparation of such a fusion polypeptide whereby an unspecified "derivative" of an amino-proximal pestivirus N^{PRO} autoprotease having an amino acid sequence that corresponds to the amino acid sequence from position 22 through position 168 of SEQ ID NO:1 will permit autoproteolytic processing to produce a free heterologous protein. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

It is agreed that no undue experimentation would be required of one of ordinary skill in the art to identify the region of a pestivirus N^{PRO} autoprotease amino acid sequence that corresponds to the region from position 22 through position 168 of SEQ ID NO:1 herein, whether a swine fever pestivirus, a bovine viral diarrhea pestivirus, or a border disease pestivirus, and can use the C-terminal autoproteolytic processing capacity of such regions of such N^{PRO} autoproteases to liberate a carboxyl-proximal fusion partner, having an amino-terminal serine, glycine or alanine, upon cleavage from an amino-proximal N^{PRO} autoprotease after expression of the fusion polypeptide in a host cell.

See Fig. 3 of Wiskerchen et al., discussed above, detected with the sequence alignments in SCORE generated with SEQ ID NO:1 in this application. Claims 1 and 4-6, however, contemplate an arbitrary number of amino acid substitutions, additions or deletions anywhere within pestivirus N^{PRO} autoprotease amino acid sequences, including modification occurring even within the core functional region corresponding to the sequence of amino acids from position 22 through position 168 of SEQ ID NO:1. See the discussion at pages 5 and 6 of the specification. Even if combined with the teachings of the prior art made of record herein, the teachings of the specification, cannot support the introduction of an unspecified number of amino acid sequence alterations in this core, functional, region of a pestivirus N^{PRO} autoprotease amino acid sequence, in any combination or any pattern. Mere sequence perturbation cannot enable the design and preparation of polynucleotides encoding a myriad of divergent pestivirus N^{PRO} autoprotease amino acid sequences that can provide the public with an autoprotease retaining its native function as required by claim 1.

It is well settled that 35 U.S.C. § 112, first paragraph, requires that a disclosure be sufficiently enabling to allow one of skill in the art to practice the invention as claimed without undue experimentation and that unpredictability in an attempt to practice a claimed invention is a significant factor supporting a rejection under 35 U.S.C. §112, first paragraph, for non-enablement. See, *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (discussing eight factors relevant to analysis of enablement). The standard set by the CCPA, the precursor of the Court of Appeals for the Federal Circuit, is not to "make and screen" any and all possible alterations because a reasonable correlation must exist between the scope asserted in the claimed subject matter and the scope of guidance the specification provides. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 25 (CCPA 1970) (scope of enablement varies inversely with the degree of unpredictability

of factors involved in physiological activity of small peptide hormone). The Federal Circuit approved this standard set by the CCPA in *Genentech, Inc. v. Novo-Nordisk A/S*, 42 USPQ2d 1001 (Fed. Cir. 1997). Applying the factors discussed in *Wands* to the disclosure of the specification, it is apparent that:

a) the specification lacks adequate, specific, guidance for altering the amino acid sequences of pestivirus N^{PRO} autoprotease amino acid sequences within the region that corresponds to the amino acid sequence from position 22 through position 168 of SEQ ID NO:1 permitted by the clauses of claims 1 and 4-6 that require this rejection,

b) the specification lacks working examples wherein any pestivirus N^{PRO} autoprotease amino acid sequence within the region that corresponds to the amino acid sequence from position 22 through position 168 of SEQ ID NO:1 is altered to the extent permitted by the claims, and

c) in view of the prior art publications of record herein, the state of the art and level of skill in the art do not support such alteration.

Thus the scope of subject matters devoid of a requirement for the core structure of a pestivirus N^{PRO} autoprotease amino acid sequence having a region corresponding to the amino acid sequence from position 22 through position 168 of SEQ ID NO:1 that is embraced by the generic phrases, ""has the autoproteolytic function of" and "derivative thereof with autoproteolytic activity", is unsupported by the present specification even if taken in combination with teachings available in the prior art.

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-13 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-13 are rejected as indefinite where claim 1 recites, "has the autoproteolytic function of", and claims 4-6 each recite, "derivative thereof with autoproteolytic activity", which recitation must inform the construction of claim 1. The phrase in claim 1 fails to indicate any characteristic other than autoproteolysis and the artisan and the public

seeking to determine the metes and bounds of the intended subject matter cannot ascertain the structure of any derivatives from the specification's disclosure, particularly where the recitations in claims 4-6 of the phrase, "derivative thereof with autoproteolytic activity", imply that some form of derivative is intended other than the successive amino-terminal amino acid sequence deletions more specifically described elsewhere in claims 5 and 6. This rejection may be overcome by deleting the term, "derivative thereof with autoproteolytic activity", in claims 4-6 and amending claim 1 to substitute the words, "is a", for the phrase, "has the autoproteolytic function of".

Claims 1-13 are rejected as indefinite because claims 1, 5, and 6 recite "polypeptide is connected to the . . . polypeptide" where the nature of the "connection" is undefined. In order that a fusion polypeptide be encoded by a claimed polynucleotide, and to allow the intended autoproteolytic cleavage, the amino-proximal pestivirus N^{PRO} autoprotease amino acid sequence region must be covalently-bound, by a peptide bond, to a carboxyl proximal heterologous polypeptide. Generic "connections", such as non-peptide bonds, will not allow the necessary autoprocessing and are probably not intended by Applicant. Claims 2-4 and 7-13 are included in this rejection because they depend from claim 1 but do not clarify its indefinite description. The specification inherently discloses the presence of a peptide bond linking an amino-proximal pestivirus N^{PRO} autoprotease to a carboxyl-proximal heterologous fusion partner and amending claims 1, 5, and 6 to state "is covalently bound", rather than "connected", will overcome this rejection of the claims.

Claims 2, 3, 5 and 6 are indefinite because each recites one or more acronyms, rendering the claims indefinite where changes in terminology may make the intended subject no longer recognizable on the basis of the acronym. Replacing each acronym with the disclosed name of the intended pestivirus, or defining each acronym at least once in the claims, e.g., in claim 2, will overcome this aspect of the rejection.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claim 1 is rejected under 35 U.S.C. § 102(e) as being anticipated by Medalbini, U.S. Patent No. 6,077,694, made of record herewith.

As noted above, claim 1 does not require that a protease having any particular structure be encoded by a claimed nucleic acid molecule, thus need not even be a pestivirus protease, an need only have autoproteolytic activity. Thus the disclosures of Medalbini of preparation of a polynucleotide encoding a fusion polypeptide, insertion of the polynucleotide in a plasmid vector suitable for expression of heterologous proteins in an *E. coli* host cell, expression of the polynucleotide in an *E. coli* host cell transformed with the vector, and subsequent recovery of a desired, or target, heterologous soluble protein liberated from the fusion polypeptide by the proteolytic processing activity of an amino-proximally-fused HIV protease upon recombinant expression in an *E. coli* host cell meets claim 1's generic limitation, "has the autoproteolytic function", where the cleavage occurs at the amino terminus of the desired, target, heterologous fusion partner. See columns 3-14 and Figure 2B.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having

ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 2-4 and 7-12 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Medalbini as applied to claim 1 above, and further view of Wiskerchen et al., made of record with Applicant's Information Disclosure Statement.

The teachings of Medalbini, discussed above, are taken as before. Medalbini does not teach the use of a pestivirus protease but teaches that any autoprocessing protease will serve in the disclosed method, at col. 5, lines 30-35, and particularly teaches that, "in some cases, the natural N-terminal sequence of the target protein may serve as the P' side of the cleavage site", in which case no portion of the HIV polymerase-derived peptide of the construct depicted in Figure 2B of Medalbini remains at the amino terminus of the heterologous polypeptide. See col. 7 at lines 63-66. Wiskerchen et al. teach that the pestivirus N^{PRO} autoprotease cleaves directly at its carboxyl terminus, liberating the rest of the RNA-virus encoded polyprotein, essentially an "homologous" fusion partner, at pages 4509-4513, and also teach a nucleic acid molecule encoding a pestivirus N^{PRO} autoprotease, see Figures 1 and 3. Wiskerchen et al. do not teach the preparation of polynucleotides encoding fusion polypeptides comprising the pestivirus N^{PRO} autoprotease other than polypeptides that comprise lesser portions of a pestivirus polyprotein.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to replace the HIV protease of Medalbini in a fusion polypeptide by preparing a nucleic acid molecule of claims 2-4 and 7 which, as noted above in the objection to the claims require no particular structure, to place the molecule in an expression vector of claims 8-10 and to then transform an *E. coli* cell of claims 11 and 12 to practice a method of claim 13 wherein the nucleic acid encodes the pestivirus N^{PRO} autoprotease instead of the HIV protease of Medalbini in a fusion polypeptide amino-proximal to a desired, heterologous, polypeptide. This is because such an artisan would have readily appreciated that Medalbini suggests doing so at at col. 5, lines 30-35, and would have

also appreciated that there would no longer be any need for a polymerase-derived linker peptide between a pestivirus N^{PRO} autoprotease, permitting the natural N-terminal sequence of an heterologous target protein to serve as the P' side of the cleavage site in every instance. Such an artisan would have experienced a reasonable expectation of success in preparing such a polynucleotide, vector, host cell, and fusion polypeptide, of claims 1-4 and 7-12, and in practicing a method of claim 13, wherein a pestivirus N^{PRO} autoprotease replaces all components of a fusion polypeptide amino-proximal to the desired, heterologous, fusion partner because the size of the HIV protease does not differ significantly from that of a pestivirus N^{PRO} autoprotease and because the autoprocessing activity of a pestivirus N^{PRO} autoprotease would require no intermediate peptide target for cleavage.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to William W. Moore whose telephone number is 571.272.0933 and whose FAX number is 571.273.0933. The examiner can normally be reached Monday through Friday between 9:00AM and 5:30PM EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's Supervisory Primary Examiner, Dr. Kathleen Kerr, can be reached at 571.272.0931. The official FAX number for all communications for the organization where this application or proceeding is assigned is 571.273.8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571.272.1600.

William W. Moore
21 September 2006

KATHLEEN M. KERR, PH.D.
SUPERVISORY PATENT EXAMINER